REMARKS

First and foremost, Applicants would like to thank Examiner Hayes for his cooperation in organizing the interview with Applicants on November 23, 2004.

After entry of this amendment, claims 2-7, 10-16, and 29, as well as the withdrawn claims 17-24 will be pending in the application.

1. INTERVIEW SUMMARY RECORD

Applicants and Applicants' representatives thank Examiner Michael Hayes for the courtesy of the recent interview on November 23, 2004 ("the Interview") in connection with the above-identified application. The Interview was attended by Examiner Michael Hayes, Dr. Ronald J. Pettis, James G. Murtha, and Applicants' representatives, Laura A. Coruzzi and Jacqueline Benn. During the interview, claim 29 as amended in view of Applicant's response to the Final Office Action dated June 15, 2004 was discussed as summarized below (37 C.F.R. §1.133 and M.P.E.P. § 713.04).

Applicants' representative presented arguments as to why claim 29 and dependent claims therefrom are enabled by the specification as filed. Applicants' representatives also presented arguments as to why the claimed invention is not anticipated by the art relied on by the Examiner. Details of these arguments are presented below.

During the Interview, Applicants' representative also discussed the Examiner's statements in an Office Action dated November 24, 2003 (Paper No. 16), whereby the Examiner indicated that references cited in an IDS filed on November 8, 2002 (Paper No. 8) were missing at the USPTO. However, the Examiner clarified that the only reference that was missing at the USPTO was reference BR (McAllister). Therefore, pursuant to the Examiner's request, Applicants submit a courtesy copy of reference BR.

2. SUMMARY OF PENDING CLAIMS

The invention described in the specification encompasses a method of drug delivery to the intradermal compartment of a subject so that improved pharmacokinetics are obtained as compared to subcutaneous delivery methods. In the embodiment claimed, the improved pharmacokinetic profile achieved exhibits a higher maximum plasma concentration and

higher bioavailability. The critical features of the claimed invention are (1) the insertion of the hollow needle so that its outlet---both the height and depth, is physically located within the intradermal compartment of the subject's skin, and (2) the application of pressure in an amount sufficient to control the rate of delivery so that the claimed enhanced pharamacokinetic profile is obtained, *i.e.,* higher maximum plasma concentration and higher bioavailability.

3. THE PENDING CLAIMS SATISFY THE REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 29 and claims dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The gravamen of the Examiner's rejection is that the claims do not recite a numerical value or a range of pressures used to achieve the claimed pharmacokinetic profile.

As discussed during the Interview, the pressure employed to control the rate of delivery in accordance with the present invention will vary depending on the nature of the formulation to be delivered. Thus, the pressure cannot be expressed in absolute numerical values or ranges. Nor is the absolute value at which pressure is applied critical to the claimed invention. Rather, this feature is captured by step (b) of claim 29 which requires, "the application of pressure in an amount effective to control the rate of delivery of the substance" so that the specified pharmacokinetic profile is achieved.

During the Interview, the Applicants explained how one skilled in the art could use the teachings of the specification to arrive at a pressure adequate to control the flow rate of any given substance or formulation, without undue experimentation. Once the optimum pressure is selected, it can thereafter be applied reproducibly to practice the invention.

For example, in order to control the rate of delivery for any given formulation, the skilled artisan could use any device described in the specification, including pumps, syringes, elastomeric membranes, osmotic pressure, and Bellville springs or washers (*see*, specification at p. 7, *ll.* 25-28). Utilizing any of the devices or means described in the specification, the skilled artisan could assay a series of pressures to determine the optimum pressure to achieve the desired pharmacokinetic profile for any given formulation. At the onset of delivery, a visual inspection for leakage or excessive weal formation at the delivery site will allow one to determine if too much pressure was applied (*see*, specification at p. 5, *l.* 22 to p. 6, *l.* 14). Subsequent to delivery, blood samples can be taken periodically to measure the concentration of the substance in the blood, until the point of clearance of the substance from the

bloodstream. The blood concentration of the substance can be plotted over time to obtain a pharmacokinetic profile which is compared to the profile resulting from subcutaneous delivery of the same substance, in order to select the optimum pressure to achieve the desired pharmacokinetic profile (*see*, specification at p. 6, *l.* 30 to p. 8, *l.* 21).

While the foregoing steps require some experimentation to work out the optimum conditions, it is routine and not undue as proscribed by *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988). In response to the Examiner's request during the Interview, we are addressing the *Wands* factors here.

Quantity of Experimentation

The issue at hand, is whether undue experimentation is required to determine the optimum pressure at which to administer the substance to achieve a specified pharmacokinetic profile. The amount of experimentation required to make this determination is not overly burdensome. Routine techniques, such as those described in the specification, are involved to apply pressure to control the rate of delivery. A series of pressures may be assayed to determine the optimum pressure to provide the desired pharmacokinetic profile. Generating a pharmacokinetic profile, also a routine technique, requires measuring blood concentrations of the substance periodically, typically from the onset of administration until the substance is cleared from the bloodstream. The pharmacokinetic profile may be graphically represented as a plot of the serum concentration over time. Once the pharmacokinetic profile is generated for a given set of conditions, such as the pressure used to control the rate of delivery, the skilled artisan can assess which conditions provide the desired profile.

Guidance Provided in the Specification

The specification provides considerable direction and guidance on how to practice the claimed invention. In particular, the specification provides that pressure can be applied to control the rate of delivery using any of the commonly known pressure generating devices, including, pumps, syringes, elastomeric membranes, osmotic pressure or Belleville springs or washers. The specification also provides that a visual inspection upon administration will provide some initial indication, *e.g.*, leakage or excessive weal formation, as to whether the appropriate pressure is being applied. The specification further provides that once the substance is administered, blood concentrations of the substance are measured over time, in order to determine if the desired pharmacokinetic profile was obtained.

Presence of Working Examples

The specification not only provides the skilled artisan with considerable direction to practice the claimed invention, it also provides working examples of the successful administration of two different substances via the claimed method. Insulin (Example 1) and parathyroid hormone (Example 2) were administered to an animal model, wherein the substances were administered to the intradermal space and pressure applied to control the rate of delivery. Blood concentrations of the substances were measured over time, pharmacokinetic profiles were generated, and in both cases, it was determined that the desired pharmacokinetic profile was obtained.

Nature of the Invention

The invention provides a solution to long standing problems with the typical methods of drug delivery, including intravenous, intramuscular and subcutaneous delivery methods. Such problems include the use of skilled health care specialists and less than desirable pharmacokinetic profiles. The claimed invention provided the recognition that improved pharmacokinetic profiles are obtainable when a substance is delivered by (1) the correct placement of a needle with the specified outlet height within the intradermal compartment, and (2) controlling the rate of delivery so that the desired pharamcokinetic profile is obtained. The specification provides routine means and devices by which pressure can be applied to control the rate of delivery. Furthermore, the specification provides examples of the routine methods used to measure the pharmacokinetic profile.

State of the Prior Art

The state of the art of drug delivery at the time the application was filed was fairly advanced. Intravenous, intramuscular and subcutaneous administrations were well established and even used commercially for drug delivery. The use of these delivery routes also routinely required assessment of the resulting pharmacokinetic profiles, a standard practice in the art at the time the application was filed.

Level of Skill in the Art

There was a high level of skill in the art of drug delivery at the time when the application was filed. All the methods needed to practice the claimed invention including drug delivery and determining pharmacokinetic profiles were well known.

Predictability or Unpredictability of the Art and State of the Art

Pharmacokinetic profiles are routinely used to evaluate optimum doses, formulations and routes of administration. Reproducibility of the pharmacokinetic profile for a given formulation and dosage regimen is expected and part of the typical experimental scheme. Such studies are routinely used for evaluating therapeutic and/or prophylactic regimens in subjects, and are typically carried out in pre-clinical and clinical phases of drug evaluation.

Breadth of the claims

The breadth of the claims is commensurate in scope with the disclosure. Steps (a) and (b) of the claimed methods are fully described and enabled by the specification, which includes the working examples that demonstrate two successful applications of the claimed methods.

Applicants respectfully submit that the *Wands* factors are met. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 29 and dependent claims therefrom under 35 U.S.C. § 112, first paragraph.

4. THE CLAIMS ARE NOT ANTICIPATED BY THE CITED ART

The patentability of the claims in view of the cited art was discusses. The art includes: Autret (Autret *et al.*, 1991 *Therapie*, 46: 5-8; "Autret"); Gross (U.S. Patent No. 5,848,991; "Gross"); and Ganderton (U.S. Patent No. 3,814,097; "Ganderton"). Each of these rejections should be withdrawn for reasons detailed below and expressed at the Interview.

None of the cited references anticipates the claimed invention, because none of the references cited disclose the pharmacokinetic profile specified by the claims, *i.e.*, higher maximum plasma concentration and a higher bioavailability.[1] The required pharmacokinetic profile is not disclosed, explicitly or inherently, in any of the cited references.

Practicing the methods of the invention results in an improved pharmacokinetic profile as compared to subcutaneous delivery. The improved pharmacokinetic profile is manifested as an improvement in at least two or more of the traditionally measured

[1] In addition, as pointed out in our previous response, the references applied against the claims do not disclose step (a) of independent claim 29.

parameters, *i.e.*, faster T_{max}, increased C_{max}, or increased AUC. Depending on the substance delivered and the rate of delivery used, different pharmacokinetic profiles may be obtained as evidenced by the accompanying declaration by co-inventor Dr. Pettis (the "Pettis Declaration"). The embodiment encompassed by the instant claims requires an increased C_{max} and an increased AUC. None of the prior art references characterize the claimed profile, expressly or inherently.

The only cited reference that discloses a pharmacokinetic profile is Autret. However, Autret does *not* disclose the pharamacokinetic profile specified in the claims. The pharmacokinetic profile disclosed by Autret (*see* Autret, Fig. 1) is (1) not improved over subcutaneous delivery (*i.e.*, the profiles are virtually identical), and (2) does *not* exhibit *both* an increased C_{max} and an increased AUC as required by the claimed invention.[2] Thus, Autret cannot anticipate the claimed invention.

The two remaining references, Gross and Ganderton, are silent as to pharmacokinetic profiles, and therefore, cannot anticipate the claims. Even if one were to stretch the disclosure of Gross to read into it the teaching of step (a) of claim 29,[3] Gross does not disclose the claimed pharmacokinetic profile and can not expressly anticipate the invention as claimed. Assuming arguendo that either Gross or Ganderton did disclose step (a), the claimed pharmacokinetic profile would not necessarily nor inevitably result, as evidenced by the data presented in the Pettis Declaration. Thus, neither Gross nor Ganderton inherently anticipate the claimed invention.

In view of the foregoing, none of the cited references anticipate the amended claims, and all rejections under 35 U.S.C. § 102(b) should be withdrawn.

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[2] Autret's characterization of the data presented supports the Applicant's position. See Autret at p. 5, Summary:

"[*n*]*either* mean plasmatic levels at each plasmatic dosage *nor* mean *areas under the curve* ... [*i.e.*, the standard measure of bioavailability]... were significantly different" when Autret's method was compared to the subcutaneous route of administration. (emphasis supplied). As summarized by Autret, "[i]n this study ... [Autret's method and subcutaneous routes of administration] ... are not different with regard to plasma levels ...".

[3] Applicant disputes the Examiner's position that Gross contains disclosure concerning needle outlet height and depth, or the criticality of its placement within the intradermal compartment, as specified in step (a) of claim 29.

CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

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SOLID AND HOLLOW MICRONEEDLES FOR TRANSDERMAL PROTEIN DELIVERY

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Introduction

Microneedles have the potential to painlessly deliver drugs across the skin at therapeutic rates. Because microneedles are just 150 μm long, they are sufficiently long to penetrate through the stratum corneum barrier, but short enough not to stimulate nerves in deeper tissue.

Previously, we reported that 20 x 20 arrays of solid silicon microneedles increased skin permeability to calcein (623 Da) up to four orders of magnitude [1]. In this study we examined the transdermal delivery of a large protein (bovine serum albumin - BSA; 66,000 Da) using solid silicon microneedles. We also tested the feasibility of microfabricating hollow needles.

Experimental Methods

Arrays of solid silicon microneedles were fabricated using a reactive ion etching process as previously described [1]. Briefly, a thin (1000 Å) layer of chromium is sputter deposited onto a silicon substrate. The chromium is then patterned into arrays of chromium circles using standard photolithography techniques, where the diameter and the center-to-center spacing of the chromium circles defines the base diameter and the tip-to-tip spacing of the microneedles. The silicon substrate is then loaded into a reactive ion etcher and exposed to a precisely controlled SF_6/O_2 plasma. The silicon is anisotropically (in the positive profile regime) etched away until the chromium masks are undercut and fall off the needle tips, leaving an array of sharp microneedles (Figure 1).

Hollow metal needles were fabricated by first encasing an array of solid silicon needles in ultra-thick UV-light photosenitive epoxy (SU-8). Removal of the needles from the epoxy left behind an epoxy mold, which was partially filled by electroplating NiFe onto the mold. The mold was then etched away, leaving behind an array of hollow conical shells (i.e., hollow needles) similar in shape to the original solid silicon microneedles.

Transdermal transport experiments were performed using heat-stripped human epidermis mounted in vertically-oriented Franz diffusion chambers. The chambers contained well-stirred phosphate buffered saline (PBS) in the receiver compartment and 100 μM fluorescein-labeled BSA in PBS in the donor reservoir. Microneedle arrays were inserted into epidermis and transdermal transport of BSA was determined by spectrofluorimetry.

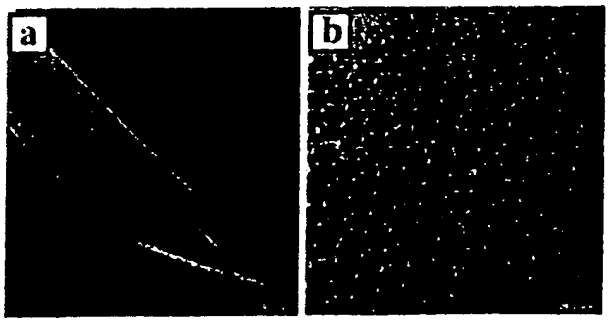

Figure 1 – A scanning electron micrograph of (a) a 26 ½ gauge syringe and (b) an array of 400 microneedles at the same magnification.

Results and Discussion

Figure 2 shows skin permeability to calcein and BSA for three experimental protocols involving transport across: (1) normal skin, (2) skin with solid microneedles embedded, and (3) skin with solid microneedles inserted for 1 hour and then removed. Passive skin permeability to BSA is below the detection limit (10^{-5} cm/h) of the spectrofluorimeter and most likely does not cross the skin at all. The permeability of human epidermis to BSA with needles inserted was determined to be 6.6 x 10^{-4} cm/h. When the microneedles were inserted for one hour and then removed, the permeability increased to 0.011 cm/h. As shown in Figure 2, the permeability to BSA is similar to that of calcein for skin treated with microneedles. The large permeability to BSA observed here is significant because macromolecules are extremely difficult to deliver across skin.

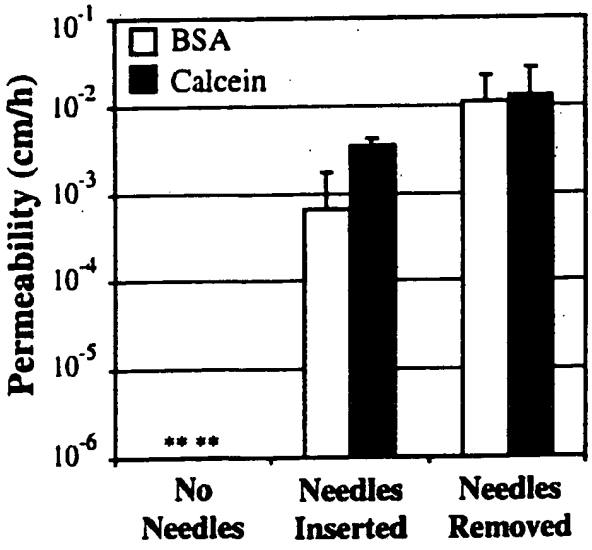

Figure 2 – Permeability of human epidermis to calcein and BSA *in vitro* for three protocols; (a) untreated skin, (b) microneedles inserted and left in skin, and (c) microneedles inserted for 1 h and then removed. (** indicates value is below the spectrofluorimeter detection limit – 10^{-6} cm/h for calcein and 10^{-5} cm/h for BSA)

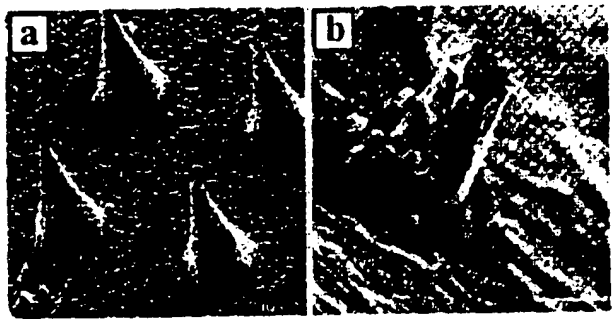

Figure 3 – A scanning electron micrograph of (a) portion of a 20 x 20 array of hollow NiFe microneedles and (b) a tip of a hollow needle penetrating up through the underside of the viable epidermis.

Hollow NiFe microneedles were fabricated using micromolding and electroplating techniques. A section of a 20 x 20 array of hollow needles is shown in Figure 2a. These microneedles are 150 μm tall, with a wall thickness of 3 μm and a 5 μm diameter hole at the tip. These microneedles are mechanically strong enough to be inserted through human epidermis with only gentle pushing. Figure 2b shows a hollow NiFe microneedle protruding up through the underside of the viable epidermis.

Conclusion

In this study, arrays of solid silicon microneedles were used to pierce human epidermis to transport BSA across the skin at dramatically increased rates. In addition hollow microneedles were fabricated using a molding technique and were shown to have sufficient mechanical strength to penetrate through human epidermis. Solid and hollow microneedles show promise as a minimally-invasive and user-friendly method to deliver drugs across skin at therapeutic rates.

References

1) Henry, S.; McAllister, D.V.; Allen, M.G.; Prausnitz, M.R. Microfabricated microneedles: A novel approach to transdermal drug delivery. *J. Pharm. Sci.* 87:922-925 (1998).